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EXAMINER	
JOYCE, CATHERINE	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 05/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/723,383	NASOFF ET AL.	
	Examiner	Art Unit	
	Catherine M. Joyce	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-74* is/are pending in the application.

4a) Of the above claim(s) *1-60 and 64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61-63,65-67 and 72-74* is/are rejected.

7)☒ Claim(s) *68-71* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. Claims 1-74 are pending, and claims 1-60 and 64 are withdrawn from consideration as drawn to a non-elected invention

2. Claims 61-63 and 65-74 are under examination.

3. Applicant's election with traverse of Group III in the reply filed on March 6, 2006 is acknowledged. The traversal is on the ground(s) that searching Groups I-III together would not pose a search burden. This argument is not found persuasive for the following reasons. The invention of group II is drawn to a method of using an anti-DR4 affinity agent while the invention of group III is drawn to an anti-DR5 affinity agent. Thus, the searches for the two inventions would not coextensive. Further, while the search for the anti-DR5 affinity agent of group III would be overlapping with a method of inducing apoptosis in a cancer cell using an anti-DR5 affinity agent, the searches would not be coextensive because a search for the affinity agent of claim 1 would entail a search for any affinity agents whether or not they induce apoptosis while a search for the invention of group I would entail a search for any mechanism of activating the DR-5 related apoptosis pathway. Thus searching any of groups I-III together would pose an undue burden. The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 61-63, 65-67, and 72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody comprising a heavy

chain variable region comprising the sequence of SEQ ID NO:4 and a light chain variable region comprising the sequence of SEQ ID NO:5, or a heavy chain variable region comprising the sequence of SEQ ID NO:8 and a light chain variable region comprising the sequence of SEQ ID NO:10, or a cell that expresses such antibodies, does not reasonably provide enablement for an antibody comprising a heavy chain variable region comprising the sequence displayed in Figure 24 (SEQ ID NO:4) or Figure 35 (SEQ ID NO:8), and a light chain variable region as displayed as in Figure 25 (SEQ ID NO:5) or Figure 35 (SEQ ID NO:10).

The claims are drawn to the following:

an affinity agent with the binding specificity of an antibody comprising a heavy chain variable region comprising the sequence displayed in Figure 24 (SEQ ID NO:4) or Figure 35 (SEQ ID NO: 8) and a light chain variable region as displayed in Figure 25 (SEQ ID NO:5) or Figure 35 (SEQ ID NO: 10) (claim 61),

which is an antibody comprising a heavy chain variable region comprising the sequence displayed in Figure 24 (SEQ ID NO:4) or Figure 35 (SEQ ID NO:8), and a light chain variable region as displayed as in Figure 25 (SEQ ID NO:5) or Figure 35 (SEQ ID NO:10) (claim 62)

wherein the affinity agent is an antibody (claim 65),

wherein the antibody is a monoclonal antibody (claim 66),

wherein the antibody is a humanized antibody (claim 67),

and

an isolated cell that expresses an antibody with the binding specificity of an antibody comprising a heavy chain variable region comprising the sequence displayed in Figure 24 (SEQ ID NO:4) or Figure 35 (SEQ ID NO:8) and a light chain variable region as displayed in Figure 25 (SEQ ID NO:5) or Figure 35 (SEQ ID NO: 10) (claim 63),

wherein the antibody is a humanized antibody (claim 72),

The specification teaches the isolation of anti-DR5 antibodies and the evaluation of these antibodies for effectivity in inducing apoptosis via an analysis of cell killing ability of the antibody on Jurkat cells (page 78, lines 21-24, and Figure 3). The specification also teaches that Antibody A had the best potency in terms of killing of Jurkat cells and that Imgenex-257 is a DR-5 specific antibody that has no functional activity (page 78, lines 22-24). The specification also teaches that the variable regions from the DR5 mouse antibody A were cloned, and the amino acid sequence of the heavy chain variable region is displayed in Figure 24 or Figure 35 and the amino acid sequence of the light chain variable region is displayed in Figure 25 or 35 (page 81, lines 14-19).

Although it is not entirely clear from the specification, it is assumed for examination purposes that the antibody V_H and V_L domains shown in figures 24 and 25, respectively, correspond to the murine Antibody A, whereas the V_H and V_L domains shown in Figure 35 correspond to the humanized form of Antibody A. A comparison of the V_H and V_L sequences is attached herewith as an Appendix to this Office Action and show that the murine V_H and humanized V_H region are not identical and that the murine V_L and humanized V_L region are not identical.

The specification cannot be extrapolated to enable the scope of the claims for the following reason that it cannot be predicted that the murine light chain variable region would function in conjunction with humaninzed heavy chain variable region, or that the murine heavy chain variable region would function in conjunction with humanized light chain variable region. Protein chemistry is probably one of the most unpredictable areas of biotechnology. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding (such as antibody CDR regions) will certainly be among the most

conserved (see Bowie et al, Science, 247:1306-1310, 1990, p. 1306, col.2). The specification provides no guidance on structure or residues that are critical to the function of the invention as claimed. Although it is clear that binding specificity of the disclosed antibody is determined by the CDR regions, it is well known that this determination requires the exquisite interaction of the CDRs and the framework region of the antibody. In particular, Gussow et al specifically teach that the applicability of antibody humanization techniques relies on, among others, the assumption that the frameworks of the variable domains serve as a scaffold to support the CDRs in a specific way that facilitates antigen binding and further teach that it is of great importance to retain the interactions between the donor CDRs and the acceptor framework as closely as possible to the CDR-framework interactions of the original Mab. Gussow et al. further teaches that the affinity of the first fully humanized antibody CAMPATH1 was nearly 40 fold lower compared to the original rat MAb, apparently because of differences of residues in the framework region of the humanized antibody compared to those of the original antibody, particularly those located close to the CDRs. Clearly, alteration of even one amino acid residue can alter the packing of the residues within the molecule as it was demonstrated that mutation of the human Ser 27 to a Phe (the residue found in the original rat antibody at this position) restored the binding affinity of the humanized antibody close to the original affinity (see page 100). Further, even minor changes in the amino acid sequence of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function (Rudikoff et al, PNAS, USA, 1982, 79: 1979). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristics of an antibody molecule. The specification provides insufficient guidance with regard to these issues and provides no working examples which demonstrate that antibodies comprising the murine light chain would function in conjunction with the humanized heavy chain to bind antigen, or that the humanized light chain would function in conjunction with the murine heavy chain to bind antigen. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

6. Claim 73 and 74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody comprising a heavy chain variable region comprising the sequence of SEQ ID NO:4 and a light chain variable region comprising the sequence of SEQ ID NO:5, or a heavy chain variable region comprising the sequence of SEQ ID NO:8 and a light chain variable region comprising the sequence of SEQ ID NO:10, or a cell that expresses such antibodies, does not reasonably provide enablement for (i) an isolated antibody comprising a complementary determining region from SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:8, or SEQ ID NO:10, or a cell that expresses such an antibody or (ii) an antibody comprising a heavy chain variable region comprising the sequence displayed in Figure 24 (SEQ ID NO:4) or Figure 35 (SEQ ID NO:8), and a light chain variable region as displayed as in Figure 25 (SEQ ID NO:5) or Figure 35 (SEQ ID NO:10).

The claims are drawn to the following:

an isolated antibody comprising a complementary determining region from SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:8 and SEQ ID NO:10 (claim 73);

and

an isolated cell that expresses an antibody comprising a complementarity determining region from SEQ ID NO:4, SEQ ID NO:8, SEQ ID NO:5 or SEQ ID NO:10 (claim 74).

The specification teaches as set forth above.

The specification cannot be extrapolated to enable the scope of the claims for the following reason that antibodies that contain only one CDR region, or that contain less the full complement of CDR regions for the described anti-DR5 antibody (Antibody) will function as contemplated. Claims 73 and 74 are drawn to an antibody, or a cell that expresses the antibody, that comprises at least one CDR region of a claimed anti-DR5 antibody and includes antibodies that comprise none, one, two or all three of the CDR regions of either/or both the light or heavy chain of the antibody. Protein chemistry is

probably one of the most unpredictable areas of biotechnology. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding (such as antibody CDR regions) will certainly be among the most conserved (see Bowie et al, Science, 247:1306-1310, 1990, p. 1306, col.2). The specification provides no guidance on structure or residues that are critical to the function of the invention as claimed. Although it is clear that binding specificity of the disclosed antibody is determined by the CDR regions, it is well known that this determination requires the exquisite interaction of the CDRs and the framework region of the antibody. The specification provides no guidance on the interaction of the at least one CDR of the claimed antibody and the rest of the structure of the antibody protein. Clearly, appropriate framework regions that house the at least one CDR is essential for providing the proper orientation for the at least one CDR to exhibit antigen specificity. Although drawn to humanization techniques, the teaching of Gussow et al (Methods in Enzymology, 1991, 203:99-121) is clearly relevant to the instant rejection. Gussow et al specifically teach that the applicability of antibody humanization techniques relies on, among others, the assumption that the frameworks of the variable domains serve as a scaffold to support the CDRs in a specific way that facilitates antigen binding and further teach that it is of great importance to retain the interactions between the donor CDRs and the acceptor framework as closely as possible to the CDR-framework interactions of the original Mab. Gussow et al. further teaches that the affinity of the first fully humanized antibody CAMPATH1 was nearly 40 fold lower compared to the original rat MAb, apparently because of differences of residues in the framework region of the humanized antibody compared to those of the original antibody, particularly those located close to the CDRs. Clearly, alteration of even one amino acid residue can alter the packing of the residues within the molecule as it was demonstrated that mutation of the human Ser 27 to a Phe (the residue found in the original rat antibody at this

position) restored the binding affinity of the humanized antibody close to the original affinity (see page 100). Further, even minor changes in the amino acid sequence of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function (Rudikoff et al, PNAS, USA, 1982, 79: 1979). Rudikoff et al teach that alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein results in the loss of antigen-binding function. Queen et al, PN-5,585,089, teach that the donor CDRs could be distorted, and the affinity of a humanized antibody could be reduced, if the amino acids immediately adjacent to the CDRs are from the acceptor human immunoglobulin (column 14, category 3). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristics of an antibody molecule. The specification provides insufficient guidance with regard to these issues and provides no working examples that would provide guidance to one skilled in the art. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

7. Claim 61 is rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

The claim is drawn to the following:

an affinity agent with the binding specificity of an antibody comprising a heavy chain variable region comprising the sequence displayed in Figure 24 (SEQ ID NO:4) or Figure 35 (SEQ ID NO: 8) and a light chain variable region as displayed in Figure 25 (SEQ ID NO:5) or Figure 35 (SEQ ID NO: 10).

Although drawn to the DNA arts, the finding in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like

a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such

characteristics." Id. at 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

While, the inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here.

Thus, the instant specification may provide an adequate written description of a "an affinity agent with the binding specificity of an antibody comprising a heavy chain variable region comprising the sequence displayed in Figure 24 (SEQ ID NO:4) or Figure 35 (SEQ ID NO: 8) and a light chain variable region as displayed in Figure 25 (SEQ ID NO:5) or Figure 35 (SEQ ID NO: 10)" per Lilly by structurally describing a representative number of species of "an affinity agent with the binding specificity of an antibody comprising a heavy chain variable region comprising the sequence displayed in Figure 24 (SEQ ID NO:4) or Figure 35 (SEQ ID NO: 8) and a light chain variable region as displayed in Figure 25 (SEQ ID NO:5) or Figure 35 (SEQ ID NO: 10)" by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe "an affinity agent with the binding specificity of an antibody comprising a heavy chain variable region comprising the sequence displayed in Figure 24 (SEQ ID NO:4) or Figure 35 (SEQ ID NO: 8) and a light chain variable region as displayed in Figure 25 (SEQ ID NO:5) or Figure 35 (SEQ ID NO: 10)" of claim 61 in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any such affinity agent, nor does the specification provide any partial structure of such affinity agent, nor any physical or chemical characteristics of the affinity agent, nor any functional characteristics coupled with a known or disclosed correlation between structure and

function, other than a single anti-DR5 antibody and variants thereof. Although the specification discloses a single anti-DR5 antibody, and variants thereof, this does not provide a description of "an affinity agent with the binding specificity of an antibody comprising a heavy chain variable region comprising the sequence displayed in Figure 24 (SEQ ID NO:4) or Figure 35 (SEQ ID NO: 8) and a light chain variable region as displayed in Figure 25 (SEQ ID NO:5) or Figure 35 (SEQ ID NO: 10)" that would satisfy the standard set out in Enzo.

The specification also fails to describe the claimed "an affinity agent with the binding specificity of an antibody comprising a heavy chain variable region comprising the sequence displayed in Figure 24 (SEQ ID NO:4) or Figure 35 (SEQ ID NO: 8) and a light chain variable region as displayed in Figure 25 (SEQ ID NO:5) or Figure 35 (SEQ ID NO: 10)" by the test set out in Lilly. The specification describes only a single anti-DR5 antibody, and variants thereof. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the "an affinity agent with the binding specificity of an antibody comprising a heavy chain variable region comprising the sequence displayed in Figure 24 (SEQ ID NO:4) or Figure 35 (SEQ ID NO: 8) and a light chain variable region as displayed in Figure 25 (SEQ ID NO:5) or Figure 35 (SEQ ID NO: 10)".

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 61, 63, 65 and 66 are rejected under 35 U.S.C. 102(b) as being anticipated by Ichikawa et al. (2001, Nature Medicine 7(8):954-960).

The claims are drawn to the following:

an affinity agent with the binding specificity of an antibody comprising a heavy chain variable region comprising the sequence displayed in Figure 24 (SEQ ID NO:4) or Figure 35 (SEQ ID NO: 8) and a light chain variable region as displayed in Figure 25 (SEQ ID NO:5) or Figure 35 (SEQ ID NO: 10) (claim 61),

wherein the affinity agent is an antibody (claim 65),

wherein the antibody is a monoclonal antibody (claim 66),

and

an isolated cell that expresses an antibody with the binding specificity of an antibody comprising a heavy chain variable region comprising the sequence displayed in Figure 24 (SEQ ID NO:4) or Figure 35 (SEQ ID NO:8) and a light chain variable region as displayed in Figure 25 (SEQ ID NO:5) or Figure 35 (SEQ ID NO: 10) (claim 63).

It is noted that while the specification does not define the phrase "with the binding specificity of", the specification states that the "the phrase 'specifically (or selectively) binds' to an antibody or 'specifically (or selectively) immunoreactive with,' when referring to a protein or peptide, refers to a binding reaction that is determinative of the presence of the protein in a heterogeneous population of proteins and other biologics'. Thus, it is assumed for examination purposes that the phrase "an affinity an affinity agent with the binding specificity of an antibody comprising a heavy chain variable region comprising the sequence displayed in Figure 24 (SEQ ID NO:4) or Figure 35 (SEQ ID NO: 8) and a light chain variable region as displayed in Figure 25 (SEQ ID NO:5) or Figure 35 (SEQ ID NO: 10)" means an affinity agent that binds to the same antigen as the anti-DR5 antibody from which the above sequences were derived.

Ichikawa teaches the isolation and characterization of a novel anti-human DR5 monoclonal antibody, TRA-8 (abstract). Ichikawa further teaches that the TRA-8 antibody was generated by immunizing mice with a DR5-higG1 fusion protein, fusing lymphocytes from the mice with myeloma cells, and screening for positive hybridomas (page 959). Ichikawa also teaches that western blot and ELISA analysis showed that the TRA-8 antibody was specific for human DR5.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 t o point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 67 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ichikawa et al. (2001, Nature Medicine 7(8):954-960) in view of Kipriyanov (1999, Molecular Biotechnology 12:173-201).

The claims are drawn to the following:

an affinity agent with the binding specificity of an antibody comprising a heavy chain variable region comprising the sequence displayed in Figure 24 (SEQ ID NO:4) or Figure 35 (SEQ ID NO: 8) and a light chain variable region as displayed in Figure 25 (SEQ ID NO:5) or Figure 35 (SEQ ID NO: 10),

wherein the affinity agent is an antibody,

wherein the antibody is a humanized antibody (claim 67),

and

an isolated cell that expresses an antibody with the binding specificity of an antibody comprising a heavy chain variable region comprising the sequence displayed in Figure 24 (SEQ ID NO:4) or Figure 35 (SEQ ID NO:8) and a light chain variable region as displayed in Figure 25 (SEQ ID NO:5) or Figure 35 (SEQ ID NO: 10), wherein the antibody is a humanized antibody (claim 72).

Ichikawa teaches as set forth above. Ichikawa also teaches that previous studies have indicated that systemic administration of the soluble form of TRAIL in animals induces tumor regression and that TRA-8 might be safer and more selective than soluble TRAIL as a therapeutic target (page 959).

Kipriyanov et al. teaches that the use of rodent antibodies for therapy poses a number of problems including the immunogenicity of the monoclonal antibodies and the

elicitation of anti-immunoglobulin response termed HAMA (human anti-murine antibody) (page 173). Kipriyanov further teaches that the limitations of monoclonal antibodies as therapeutic agents has been addressed by genetic engineering to create humanized antibodies wherein much of the rodent-derived sequence is replaced with sequences derived from human immunoglobulins without loss of function, antibodies were murine and were recognized as foreign by patients leading to human anti-mouse antibody (HAMA) responses (page 173). Kipriyanov also teaches a number of cell based expression systems for the production of the recombinant humanized antibodies (pages 176-177).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to humanize the TRA-8 antibody of Ichikawa in accordance with the methods of Kipriyanov, and to create an isolated cell that expresses the humanized TRA-8 antibody, and one of skill in the art would have been motivated to do so, because of the therapeutic potential of the anti-DR5 antibodies and the specific affinity of the murine TRA-8 antibody as described in Ichikawa and the known problems associated with the use of wholly rodent antibodies for human therapeutics. One of skill in the art would have had a reasonable expectation of success in humanizing the TRA-8 antibody because, as described in Kipriyanov, the techniques for generating such antibodies are well known in the art.

12. Claims 68-71 are objected to as being dependent on a rejected base claim. Claims 68-71 would be allowable if written in independent form.

13. No claims are allowed.

Conclusion

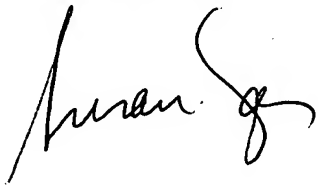
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine M. Joyce whose telephone number is 571-272-3321. The examiner can normally be reached on Monday thru Friday, 10:15 - 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Catherine Joyce
Examiner
Art Unit 1642

SUSAN UNGAR, PH.D
PRIMARY EXAMINER



GenCore version 5.1.7

OM protein - protein search, using sw model

Run on: April 25, 2006, 16:30:11 ; Search time 0.001 Seconds
(without alignments)
13.924 Million cell updates/sec

Title: us-10-723-383-4
Perfect score: 636
Sequence: 1 KVQLQQSGAELVKPGASVKL.....HEEGIYFDYWGQGTTLTVSS 118

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 1 seqs, 118 residues

Total number of hits satisfying chosen parameters: 1

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : us-10-723-383-8:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	629	98.9	118	1	us-10-723-383-8	

ALIGNMENTS

RESULT 1
us-10-723-383-8

Query Match 98.9%; Score 629; DB 1; Length 118;
Best Local Similarity 99.2%; Pred. No. 0;
Matches 117; Conservative 0; Mismatches 1; Indels 0; Gaps 0;

```
Qy          1 KVQLQQSGAELVKPGASVKLSCKASGYTFTDYTIHWVKQRSGQGLEWIGWFYPGGGYIKY 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 KVQLQQSGAELVKPGASVKLSCKASGYTFTDYTIHWVKQRSGQGLEWIGWFYPGGGYIKY 60

Qy         61 NEKFKDRATLTADKSSNTVYMELSRLTSEGSAVYFCARHEEGIYFDYWGQGTTLTVSS 118
              |||||||||||||||||||||||||| ||||||||||||||||||||||||||
Db         61 NEKFKDRATLTADKSSNTVYMELSRLTSEDSAVYFCARHEEGIYFDYWGQGTTLTVSS 118
```

Search completed: April 25, 2006, 16:30:11
Job time : 0.001 secs

GenCore version 5.1.7

OM protein - protein search, using sw model

Run on: April 25, 2006, 16:31:11 ; Search time 0.001 Seconds
(without alignments)
11.336 Million cell updates/sec

Title: us-10-723-383-5
Perfect score: 576
Sequence: 1 DIAMTQSHKFMSTLVGDRVS.....QWSSNPLTFGAGTKLELKRA 109

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 1 seqs, 104 residues

Total number of hits satisfying chosen parameters: 1

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : us-10-723-383-10:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	490	85.1	104	1	us-10-723-383-10	

ALIGNMENTS

RESULT 1
us-10-723-383-10

Query Match 85.1%; Score 490; DB 1; Length 104;
Best Local Similarity 88.5%; Pred. No. 0;
Matches 92; Conservative 4; Mismatches 8; Indels 0; Gaps 0;

```
Qy          1 DIAMTQSHKFMSTLVGDRVSITCKASQDVNTAIAWYQQKPGQSPKLLIYWASTRHTGVPD 60
              || |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||
Db          1 DIVMTQSHKFMSTSVGDRVSITCKASQDVNTAIAWYQQKPGQSPKLLIYWASTRHTGVPD 60

Qy         61 RFTGSGSGTDYTLTISSMEAEDAATYYCQQWSSNPLTFGAGTKL 104
              ||||||||||||||||::||| | ||||| : | |||:||||
Db         61 RFTGSGSGTDYTLTISSVQAEDLALYYCQQHYTTPPTFGSGTKL 104
```

Search completed: April 25, 2006, 16:31:11
Job time : 0.001 secs